

PREVENTING AIRWAY MUCUS PRODUCTION BY ADMINISTRATION OF EGF-R ANTAGONISTS

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This APPLICATION is A CIP OF 09/375,597, now USPN 6,270,747, which CLAIMS benefit OF 60/097,023, filed 8/18/98.

GOVERNMENT RIGHTS

5 The United States Government may have certain rights in this application pursuant to Grant HL-24136 awarded by the National Institutes of Health Program.

FIELD OF THE INVENTION

10 This invention relates generally to the field of pulmonary treatment. More particularly, the invention relates to inhibiting hypersecretion of mucus in lungs and airways by the administration of an EGF-R antagonist. In addition, this invention also relates to methods for the development or assessment of candidate agents capable of inhibiting hypersecretion of mucus in the lungs.

BACKGROUND OF THE INVENTION

15 In the conducting airways of the respiratory system, the mucociliary system serves as the primary defense mechanism to move inhaled particles or infectious agents out of the airways in the lungs. In addition, substances present in airway fluids serve to limit the toxicity of the particles and to inactivate infective agents. The physical mechanism of coughing serves to expel the mucus from the airway passages (see e.g., "Foundations of Respiratory Care," Pierson and Kacmarek, eds. (1992) Churchill Livingstone Inc. New York, New York; "Harrison's Principles of Internal Medicine", Fauci et al., eds. (1997) 20 14th Edition, McGraw Hill, New York, New York).

25 The mucociliary system consists of ciliated epithelial cells, epithelial goblet cells, and serous and mucous cells located in submucosal glands. The cilia are surrounded by an aqueous layer (periciliary fluid) secreted into the lumen of the airway passage by the active transport of chloride and the passive movement of water across the epithelium. The cilia make contact with the mucus floating on this aqueous layer, and via a unidirectional propelling motion provide for movement of mucus toward the glottis (see Pierson and Kacmarek, *supra* and Fauci, et al., *supra*). Mucus is produced by the epithelial goblet cells and submucosal gland cells and is secreted into the lumen of the airway after degranulation.

30 While mucus generally facilitates the clearance of inhaled particles or infectious agents, hypersecretion of mucus in the airways may cause progressive airway obstruction. In peripheral airways, cough is ineffective for clearing secretions. Furthermore, because of their small dimensions, small airways containing many goblet cells are especially vulnerable to airway plugging by mucus. Airway hypersecretion affects a substantial number of individuals; it is seen in a variety of pulmonary diseases, such as chronic bronchitis, acute asthma, cystic fibrosis, and bronchiectasis.

Figure 5 is a graph depicting the effect of EGF-R tyrosine kinase inhibitor (BIBX1522) on production of goblet cells (expressed as % of stained area of airway epithelium occupied by Alcian blue/PAS-positive stained cells).

5 Figure 6 is a bar graph depicting tissue distribution of EGFR immunoreactivity in healthy and in asthmatic airway epithelial cells.

Figure 7 is a graph depicting correlation between EGFR immunoreactivity and MUC5AC production in airway epithelium.

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Figure 8 is a graph depicting the dose-dependent effect of IL-13 instillation on percent area of Alcian blue (AB)/PAS staining (Figure 8A) and MUC5AC protein expression (Figure 8B) in rat airways.

15 Figure 9 is a graph depicting dose-dependent inhibition of IL-13-induced staining of mucous glycoconjugates with Alcian blue/PAS (Figure 9A) and MUC5AC (Figure 9B) by a selective EGFR tyrosine kinase inhibitor, BIBX 1522, in rats.

20 Figure 10 is a graph depicting the effect of IL-13 instillation on leukocyte recruitment (Figure 10A) and Alcian blue (AB)/PAS staining (Figure 10B) in rat airway epithelium.

Figure 11 is an autoradiograph depicting tyrosine phosphorylation of EGFR induced by cigarette smoke and by TGF α . Results are representative of three different experiments. Bar = 170 kD.

25 Figure 12 is a bar graph depicting the effect of incubation of cigarette smoke solution with NCI-H292 cells, and the effects of ^{tyrosine}tyrosine kinase inhibitors and of antioxidants on MUC5AC protein synthesis induced by cigarette smoke.

30 Figure 13 is a bar graph depicting the effect of inhalation of cigarette smoke on percentage of Alcian blue/PAS-stained area of airway epithelium, and the effect of an EGFR tyrosine kinase inhibitor on cigarette smoke-induced Alcian blue/PAS response in pathogen-free rats.

Figure 14 is a bar graph depicting the effect of inhalation of cigarette smoke on MUC5AC mRNA expression in tracheobronchial tissue in pathogen-free rats, and the effect of an EGFR ^{tyrosine}tyrosine kinase inhibitor on cigarette smoke-induced MUC5AC mRNA expression.